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The feasibility of muscle mitochondrial respiratory chain phenotyping across the cognitive spectrum in Parkinson's disease

Alison J. Yarnall[a,b], Antoneta Granic[b,c], Samantha Waite[a], Kieren G. Hollingsworth[a,d], Charlotte Warren[a,e], Amy E. Vincent[a,e], Doug M. Turnbull[a,e,f], Robert W. Taylor[a,e,f], Richard M. Dodds[b,c], Avan A. Sayer[b,c,*]

[a] Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom
[b] NIHR Newcastle Biomedical Research Centre, Newcastle University and Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom
[c] AGE Research Group, Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle upon Tyne, United Kingdom
[d] Newcastle Magnetic Resonance Centre, Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle-upon-Tyne, United Kingdom
[e] Wellcome Trust Centre for Mitochondrial Research, Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, United Kingdom
[f] Newcastle NHS Highly Specialised Mitochondrial Diagnostic Laboratory, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom

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ABSTRACT

Introduction: There has been little work on the relationship between sarcopenia, a progressive skeletal muscle disorder, and age-related neurodegenerative diseases such as Parkinson's disease (PD).
Objectives: We aimed to determine: 1) the feasibility of characterizing skeletal muscle across a range of cognitive function in PD; 2) if muscle mitochondrial respiratory chain (MRC) function and content are preserved in older adults with PD.
Methods: Sarcopenia was defined using handgrip strength, chair rise and bioimpedance analysis. MRC function was assessed using phosphorous magnetic resonance spectroscopy (MRS) by estimating $\tau_{1/2}$ PCr (s) (phosphocreatine half-time recovery) in the calf muscles following a bout of aerobic exercise. Biopsy of the vastus lateralis muscle was performed, and MRC content assessed by fluorescent immunohistochemistry for porin and components of MRC Complexes I and IV.
Results: Nine participants (78% male; mean age 79.9; PD duration 3.3 years) were recruited. Four had cognitive impairment. Six participants had probable sarcopenia. Eight participants completed MRS and had mean (SD) $\tau_{1/2}$ PCr of 37.8 (7.6) seconds, suggesting preserved mitochondrial function. Muscle biopsies were obtained in all and the procedure was well tolerated. Porin Z-score, a proxy for mitochondrial mass, was lower than expected compared to controls (0–89% of fibres with low porin). There was a small amount of Complex I (0.16–4.59%) and Complex IV (0–3.79%) deficiency.
Conclusions: Detailed phenotyping, muscle biopsy and imaging was feasible and acceptable across a spectrum of cognitive function in PD. Sarcopenia was relatively common and may be associated with lower mitochondrial mass and low levels of MRC deficiency.

1. Introduction

The prevalence of Parkinson's disease (PD) and thus the burden of its associated symptoms will increase in future years due to secular trends in the age-structure of populations (GBD 2016 Parkinson's Disease Collaborators, 2018). Optimizing health in older age is therefore of utmost importance in terms of health and social care costs and prevention of morbidity and mortality associated with the disease. An understanding of the mechanisms which govern both healthy and adverse aging in PD would permit the more effective use of interventions in the disorder.

Sarcopenia, a progressive and generalized muscle disorder with accelerated loss of muscle strength and mass (Cruz-Jentoft et al., 2019; Cruz-Jentoft and Sayer, 2019) leading to impaired function (Cruz-

* Corresponding author at: AGE Research Group, Translational and Clinical Research Institute, Newcastle University, and NIHR Newcastle Biomedical Research Centre, Newcastle University and Newcastle upon Tyne Hospitals NHS Foundation Trust, Campus for Ageing and Vitality, Biomedical Research Building, Newcastle upon Tyne NE4 5PL, United Kingdom.
E-mail address: avan.sayer@newcastle.ac.uk (A.A. Sayer).

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Jentoft et al., 2019; Cruz-Jentoft and Sayer, 2019; Cruz-Jentoft et al., 2010), is a major focus for translational research, and is most frequent in older age groups (Cruz-Jentoft et al., 2014; Dodds et al., 2017). Its identification is of vital importance due to the association with adverse health outcomes (Beaudart et al., 2017) and strong evidence base for resistance exercise in its primary treatment (Dent et al., 2018). To date, there has been a paucity of work on how sarcopenia may interrelate to age-related neurological diseases such as PD. Preliminary work suggests that accelerated muscle loss may start early in the neurodegenerative disease process, with an association highlighted between early stage sarcopenia and motor dysfunction in a prodromal PD cohort (Drey et al., 2017). This is supported by earlier work demonstrating that low handgrip strength, a key parameter of sarcopenia in the revised European Working group on Sarcopenia in Older People (EWGSOP2) guidelines (Cruz-Jentoft et al., 2019), is associated with increasing severity of PD (Roberts et al., 2015). Studies in established PD have found a higher prevalence of sarcopenia than controls (Peball et al., 2019; Tan et al., 2018), although lacked the extensive phenotyping to elicit potential underlying neurobiological mechanisms.

There is good evidence that bioenergetic abnormalities exist in PD; in this context, mitochondrial dysfunction is of particular importance. Neurons are reliant on mitochondrial integrity and have high rates of metabolic activity, especially in presynaptic and postsynaptic sites (Exner et al., 2012). Mitochondrial dysfunction has also been implicated in the development of sarcopenia (Brierley et al., 1996; Joseph et al., 2012; St-Jean-Pelletier et al., 2017), although recent work found preservation of muscle mitochondrial respiratory chain (MRC) function and content in healthy, active 85-year-olds (Dodds et al., 2018). A number of historic studies have demonstrated mitochondrial abnormalities in PD in non-neuronal tissue (Bindoff et al., 1991; Blin et al., 1994; Ercan et al., 2009), but the role of skeletal muscle mitochondrial abnormalities in PD in relation to sarcopenia or physical performance has not yet been evaluated.

In view of the absence of mechanistic studies of older patients with PD where detailed phenotyping, muscle biopsy and imaging are analyzed, the aims of this study were to determine: 1) the feasibility of obtaining and characterizing muscle in older adults with PD, including phosphorous magnetic resonance spectroscopy (^{31}P-MRS) and skeletal muscle biopsy; and 2) if skeletal muscle MRC chain function and content are preserved in those with and without sarcopenia across a range of cognition.

2. Methods

2.1. Participants and assessments

Participants with PD, diagnosed by a movement disorder specialist according to the Queen Square Brain Bank criteria (Hughes et al., 2002), and stable on current medication for a minimum of four weeks were recruited from the Newcastle upon Tyne NHS Foundation Trust Parkinson's service. Exclusion criteria comprised individuals with a cardiac pacemaker *in situ* or any other metallic or programmable device; those unable to give informed consent; those taking anticoagulant or antiplatelet drugs that were unable to be temporarily stopped; and those considered inappropriate to approach according to their treating clinician. All participants had capacity to provide written informed consent, and the study was approved by the Tyne & Wear South Research Ethics Committee (17/NE/0150), UK and conformed to the principles of the Declaration of Helsinki.

General demographic data including disease duration, past medical history and current medication (including levodopa equivalent daily dose (LEDD; mg/day) (Tomlinson et al., 2010) were obtained from participants. Motor function was evaluated using the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (Goetz et al., 2008), mood was assessed with the 15-item Geriatric Depression Scale (GDS) (Yesavage et al., 1982), and global cognition with the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) tools. Participants were defined as having normal cognition, mild cognitive impairment (PD-MCI; based on Level I Movement Disorder Society criteria (MoCA < 26/30 plus decline noted by participants/family/treating clinician with no evidence of impact on activities of daily living (ADLs) (Litvan et al., 2012), or mild PD dementia (PDD; according to Movement Disorder Society Task Force Criteria for PDD) (Emre et al., 2007). Self-reported difficulties or needing help with 17 ADLs such as dressing/undressing, cutting toenails, shopping and managing finances was enquired from participants. The Short Form 36 (SF-36) Health Survey Questionnaire was used to derive general health and physical functioning scores (Ware Jr. and Gandek, 1998). Self-reported physical activity was assessed using the rapid assessment of physical activity (RAPA), deriving scores for aerobic activity (1–7, with 7 being most active) and strength and flexibility activity (0–3, with 3 most being active) (Topolski et al., 2006). Height and weight were used to calculate body mass index (BMI). Ambulatory activity was objectively measured in the home using body worn sensors using the validated Axivity movement sensor (AX3; Axivity, York, UK; 100 Hz, ± 8 g), with a sampling frequency of 100 Hz. Outcomes measured for accelerometry data were in keeping with previous work (Lord et al., 2013).

2.2. Identifying sarcopenia

Handgrip strength (kg) was measured with a Jamar handheld hydraulic dynamometer (Promedics, UK) using three trials in both hands following a standard protocol (Roberts et al., 2011) and using the maximum value obtained for analyses. Chair stand test (5-times sit-to-stand) and 4-meter gait speed (m/s) were also measured using standardized protocols. Assessments were performed whilst "on" medication. Height (cm), body weight (kg) and bioimpedance were assessed using TANITA TBF-300 MA (TANITA Corporation, Tokyo, Japan). Whole body impedance (*R*; ohms) was used to estimate skeletal muscle (SM) mass using the formula: SM mass (kg) = $[(Ht^2/R \times 0.401) + (\text{gender} \times 3.825) + (\text{age} \times -0.071)] + 5.102$ (Janssen et al., 2000). Skeletal muscle index (SMI; kg/m^2) was calculated from SM mass divided by height squared, with a cut-off as ≤10.75 kg/m^2 in men and ≤6.75 kg/m^2 in women considered as low lean mass (Cruz-Jentoft et al., 2010).

Probable sarcopenia was defined using the EWGSOP2 guidelines: handgrip strength < 27 kg in men or < 16 kg in women, and/or chair stand > 15 s for five rises (Cruz-Jentoft et al., 2019). Confirmed sarcopenia was present in participants who also had low SMI, and severe sarcopenia in those who also had both low SMI and a gait speed ≤0.8 m/s.

2.3. Phosphorous magnetic resonance spectroscopy

Participants attended ^{31}P-MRS scanning and performed a low-intensity plantar flexion exercise in the scanner with incremental loading, until the phosphocreatine in the gastrocnemius and soleus muscles was depleted by approximately 50%. Measurements were taken every 10 s during exercise and recovery. An exponential recovery curve was fitted to the area under the phosphocreatine peak from which we modelled the time taken, $\tau_{1/2}$ PCr (seconds), for recovery halfway to baseline, as a measure of mitochondrial oxidative function, with shorter times implying higher function (Hollingsworth et al., 2008).

2.4. Muscle biopsy

Biopsy of the vastus lateralis muscle was obtained under local anaesthesia from all participants using a Weil Blakesley conchotome. The samples were snap frozen in isopentane cooled in liquid nitrogen.

2.5. Quadruple immunofluorescence

Two 10 μm sections from each biopsy were used for the quadruple immunofluorescence with antibodies to laminin, NDUFB8 (subunit of Complex I), MTCOI (subunit of Complex IV) and porin, as described previously (Dodds et al., 2018; Rygiel et al., 2017). Control samples were biopsies obtained from three younger patients undergoing orthopaedic surgery (males aged 20 and 24; female aged 23 years). The control and participant sections were reacted the same day with the same batch of antibody and identical concentrations. All exposure times were set and maintained throughout the imaging.

The immunofluorescence data from the fibres in the control samples were used to produce linear regression models for the relationships between levels of Complex I and porin, and between Complex IV and porin. The regression findings were then used to predict the expected levels of Complex I and IV per fibre among study participants based on the fibres' measured porin levels. The measured values in Complex I and IV were then expressed as Z-scores. Porin values in the fibres of study participants were also expressed as Z-scores, that is, expressed relative to the values seen in the control samples (which were defined as having a mean of 0 and standard deviation (SD) of 1). The percentages of deficient fibres (range) were calculated as the sum of the intermediate positive, intermediate negative, and negative fibres for each sample. Deficient fibres were defined as those deviating from the normal expected expression (Complex I and Complex IV, porin) in the controls.

2.6. Statistics

Descriptive statistical analyses were calculated for variables of interest in SPSS version 24.

3. Results

3.1. Participants

Of the 13 participants approached, nine consented and all completed the entire assessments. Reasons for non-participation were medically unwell or not interested in research. The mean age of participants was 79.9 (± 6.2) years; two were female; and mean disease duration was 3.3 years (range 1.6–5.6) (Table 1). Two (22.2%) were diagnosed with PDD, 22.2% had PD-MCI and five were cognitively normal.

3.2. Feasibility, acceptability and overall findings for muscle mitochondrial function and content

It was possible to attempt the MRS protocol in all, with all but one participant achieving sufficient depletion of phosphocreatine by exercising. Mean $\tau_{1/2}$ PCr was 37.8 (7.6) seconds, which was slightly higher than previously seen by our group in healthy 85 year-olds (Dodds et al., 2018), but not significantly so. It was also possible to obtain muscle tissue in all participants, with no complications noted at the follow-up visit. Analysis of mitochondrial respiratory chain levels demonstrated a small amount of Complex I (0.15–4.59% of fibres; mean 0.49 (SD 0.98) Z-score) and Complex IV (0–3.79% of fibres; mean −0.12 (SD 0.81) Z-score) deficiency (Table 1, Fig. 1.). The majority of patients also showed a reduction in mitochondrial mass (0–89.3% of fibres; mean porin Z-score of 0.90 (SD 1.28)), with over half (5 out of 9) patients having > 20% of fibres classified as low porin (Table 1, Fig. 1.).

3.3. Sarcopenia status

Six participants had weak handgrip and/or chair rise (probable sarcopenia), with two of these also having low SMI (confirmed sarcopenia). Of the two with confirmed sarcopenia, one also had a gait speed ≤0.8 m/s, indicating severe sarcopenia. Those with probable/confirmed sarcopenia tended to be older (81.8 *vs.* 76.1 years), with greater motor scores (MDS-UPDRS 3 27.2 *vs.* 21.0), lower cognitive scores (MMSE 26.7 *vs.* 28.7; MoCA 21.5 *vs.* 25), and lower BMI (23.7 *vs.* 27.0) than those without sarcopenia. Four of the six with probable/confirmed sarcopenia had PD-MCI or PDD, whereas all participants with normal muscle function had normal cognition. PD duration (3.3 *vs.* 3.2 years), LEDD (438.8 *vs.* 421.7 mg/day), SF36 physical functioning (72.5 *vs.* 75) and SF36 general health (64.2 *vs.* 60) were similar in those with and without sarcopenia, respectively. All but one participant had usable accelerometry data. Self-reported activity scores for aerobic (4.5 *vs.* 5) and strength and flexibility (0.3 *vs.* 0.6) were similar across the groups; a finding that was corroborated by objective Axivity measures (mean steps per day 11,632 *vs.* 12,250; walk time per day 155.9 *vs.* 164.4 min). With respect to mitochondrial function and content in those with and without sarcopenia, Z-scores for Complex I (0.20 *vs.* 1.06, respectively) and Complex IV (−0.24 *vs.* 0.12, respectively) were greater in those with normal muscle function. Z-scores for porin (−0.97 *vs.* −0.75, respectively) were broadly analogous, although in the sarcopenia group two participants had Z-scores greater than three SD below normal. Recovery times from ^{31}P-MRS scanning were comparable across the groups ($\tau_{1/2}$ PCr 36.9 *vs.* 40.7 s).

4. Discussion

This study represents the first comprehensive muscle phenotyping of participants with PD across a spectrum of cognition, and demonstrates that phosphorous magnetic resonance spectroscopy and muscle biopsy is feasible and safe in older patients with and without cognitive impairment. In this small cohort of participants from secondary care, sarcopenia was common and there was some evidence of reduced skeletal muscle mitochondrial content. The study of sarcopenia in long-term conditions such as PD is paramount to understanding potential cellular and molecular mechanisms of sarcopenia, to enable better direction of future interventions.

In keeping with recent prevalence studies of sarcopenia in PD (Lima et al., 2020; Peball et al., 2019; Vetrano et al., 2018; Yazar et al., 2018), probable/confirmed sarcopenia was a frequent occurrence and was present in two-thirds of participants. Although a minority of studies have demonstrated lower prevalence (Barichella et al., 2016; Tan et al., 2018), sarcopenia diagnosis is dependent on definition used, with one study in PD demonstrating little agreement among different criteria evaluated (Vetrano et al., 2018). Our study is one of the few studies to utilize the new EWGSOP2 guidelines to identify sarcopenia within neurodegenerative disease (Lima et al., 2020). Further novelty is reflected in the breadth of cognitive status seen in our participants, demonstrating the feasibility of deep phenotyping even in those with early PDD. All of those with either PD-MCI or PDD had probable/confirmed sarcopenia, with one of the PDD participants reaching “severe” status. Caution is required, however, in interpreting these results, due to the small numbers within the subgroups. To date there has been a paucity of work on the interrelationship between dementia and sarcopenia, despite potential shared underlying mechanisms such as neuroinflammation (Drey et al., 2017). This is particularly evident in Lewy body dementia, with no studies to date examining muscle function.

To our knowledge, this is the first study of ^{31}P-MRS of the gastrocnemius and soleus muscles in older PD participants. We have demonstrated that this is feasible and well tolerated, with all but one participant attaining sufficient depletion of phosphocreatine during exercise. Two historic studies in PD utilised MRS of the forearm with conflicting results regarding muscle energetics (Taylor et al., 1994; Penn et al., 1995), although mean age was much younger, and sarcopenia was not the focus in either study. The mean $\tau_{1/2}$ PCr in our sample was largely in keeping with preserved mitochondrial oxidative capacity in calf muscle, although slightly longer than seen in a small sample aged 70–83 years (32 s) (Taylor et al., 1997) and healthy

Table 1
Summary of characteristics of study participants.

General			PD specific				Sarcopenia-related							Activity	Mitochondrial deficiency % of fibres and (Z-score)			Mitochondrial function
ID	Sex	Age (year)	PD duration (year)	LEDD (mg/d)	MDS UPDRS3	PD-CN/ MCI/ PDD	Handgrip strength (kg)	Chair rise (s)	BMI (kg/ m^2)	Estimated SMM	Estimated SMI (kg/m^2)	Gait speed (m/s)	Sarcopenia status	Walk time/ day (min)	Complex I	Complex IV	MM (Porin)	$Tau_{1/2}$ PCr (s)
1	F	85.9	5.2	584	31	PD-NC	20	22.66	28.3	22.2	9.2	0.70	Probable	95.7	0.38 (−0.58)	1.52 (−1.32)	0.68 (0.20)	36.5
2	M	73.4	3.3	250	25	PD-MCI	34	15.58	24.2	25.8	8.9	1.10	Confirmed	199.4	2.65 (−0.27)	0.13 (0.06)	0.00 (0.77)	26.0
3	M	84	1.6	599	39	PD-NC	14	35.06	20.9	35.9	11.7	0.50	Probable	106.2	1.12 (2.03)	0.00 (1.02)	89.33 (−3.08)	36.6
4	M	80	5.2	675	19	PD-MCI	42	15.80	26.1	37.7	12.3	1.10	Probable	288.3	1.79 (−0.21)	0.39 (−1.11)	0.31 (0.17)	30.7
5	F	85.9	2.8	300	15	PDD	24	15.03	20.3	17.3	7	0.70	Probable	89.9	0.37 (0.42)	0.62 (0.09)	58.26 (−2.32)	44.9
6	M	71.2	2.3	300	28	PD-NC	46	12.76	29.1	27.6	9.5	1.20	Normal	162.7	1.10 (1.51)	0.10 (−0.20)	4.84 (−0.21)	46.6
7	M	71.7	5.6	965	21	PD-NC	46	12.00	22.7	32.3	10.7	1.40	Normal	243.5	0.16 (1.68)	0.16 (1.05)	24.69 (−1.27)	Insufficient depletion of PCr
8	M	81.7	1.9	225	34	PDD	22	15.50	22.6	26.3	8.9	0.80	Confirmed; severe	Data not captured	4.59 (−0.18)	3.76 (−0.15)	27.08 (−1.57)	46.4
9	M	85.4	1.7	0	14	PD-NC	36	11.09	29.1	30.3	9.9	0.80	Normal	86.9	4.52 (0.00)	2.26 (−0.49)	21.32 (−0.77)	34.7

Abbreviation: BMI, body mass index; LEDD, mean levodopa equivalent daily dose; MCI, mild cognitive impairment; MDS UPDRS 3, Movement Disorder Society Unified Parkinson's Disease Rating Scale Part 3; MM, mitochondrial mass; PD, Parkinson's disease; PD-CN, Parkinson's disease cognitively normal; PDD, Parkinson's disease dementia; SMI, skeletal muscle index; SMM, skeletal muscle mass.

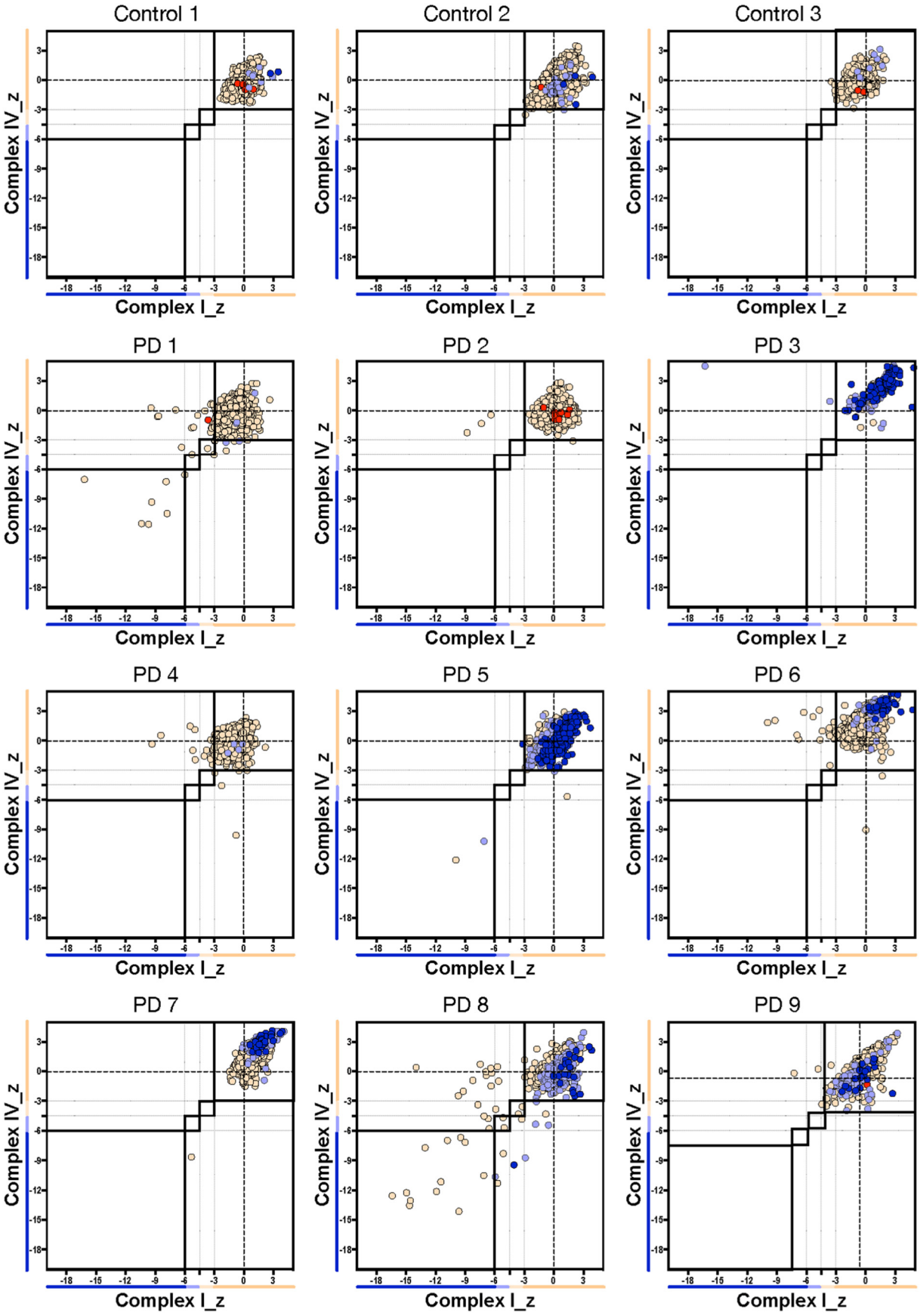

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Fig. 1. Mitochondrial respiratory chain expression profiles (complex I, complex IV and mitochondrial mass (porin) Z-scores) in controls and PD patients.
Each point represents the measurement from an individual muscle fibre, color-coded to reflect its mitochondrial mass (very low: blue; low: light blue; normal: light orange; high: orange, and very high: red). Thin black dashed lines indicate the SD used to classify fibres; lines next to x and y axis indicate the levels of Complex I and Complex IV, respectively (beige: normal; light beige: intermediate positive; light blue: intermediate negative, and blue: negative). Bold dashed lines designate the mean expression level of normal fibres.
Abbreviations: Complex I_z (Complex I Z-score); Complex IV_z (Complex IV Z-scores); PD 1-9, Parkinson's disease patients 1 to 9.

85 year-olds (35.6 s) (Dodds et al., 2018). It is noteworthy that two of the three participants with longer (> 44 s) $\tau_{1/2}$ PCr values had sarcopenia. A possible explanation for the largely normal values seen in our study, despite high prevalence of sarcopenia, is the subjective and objective evidence of engagement in physical activity (average steps per day > 10,000), which demonstrably improves mitochondrial capacity in non-PD patients (Distefano et al., 2018).

In keeping with previous work from our group in community-dwelling older adults, primarily MRC positive fibres were seen on quadruple immunofluorescence (Z-score ≥ −3) (Dodds et al., 2018; Rygiel et al., 2017). Complex I and IV deficient fibres were present at < 5% in all patients, which is comparable to previous findings in aged muscle (Brierley et al., 1998). Mitochondrial mass (*i.e.* porin as a marker) was also low in the majority of patients. Although this is expected in aging, the degree of mitochondrial depletion observed here was slightly higher than previously reported, including in healthy 85 year-olds (Dodds et al., 2018). All participants agreed to undergo muscle biopsy, which was well tolerated with no complications reported.

4.1. Study strengths and limitations

Strengths of this work include the successful recruitment rate of this detailed study, including muscle phenotyping and sarcopenia status across a range of cognition in participants with PD. Our recent study of a healthy 85-year-old group provided a comparison to ensure the mitochondrial changes were not solely an effect of age (Dodds et al., 2018). Limitations include the small sample size, precluding the analysis of associations between mitochondrial function and measures of sarcopenia, cognitive assessments or disease severity. The inclusion of chair rise as a measure of low strength may be confounded by bradykinesia and rigidity seen in PD; although this was minimized by ensuring participants were assessed in their “on” state.

In conclusion, sarcopenia was common in a small cohort of PD participants with MCI and PDD, and was associated with possible changes in mitochondrial content. Detailed muscle phenotyping was feasible and well tolerated, and provides potential evidence of the mechanisms that may underpin sarcopenia in this neurodegenerative disease.

Declaration of competing interest

The authors report no conflict of interest.

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Authors' contribution statement

Alison J. Yarnall: Conceptualization, Methodology, Formal analysis, Investigation, Data collection, Writing – original draft, Project administration; **Antoneta Granic**: Methodology, Investigation, Data curation, Writing – review & editing, Resources, Data interpretation; **Samantha Waite**: Formal analysis, Writing – original draft; **Kieran Hollingsworth**: Writing – review & editing, Data interpretation; **Charlotte Warren**: Methodology, Writing – review & editing, Formal analysis, Visualization, Data Interpretation; **Amy E. Vincent**: Methodology, Writing – review & editing, Visualization; **Doug M. Turnbull**: Methodology, Writing – review & editing; **Robert W. Taylor**: Methodology, Writing – review & editing, Data interpretation; **Richard M. Dodds**: Investigation, Writing – review & editing, Data interpretation; **Avan A. Sayer**: Conceptualization, Funding acquisition, Supervision, Resources, Writing – review & editing.

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